Assessment of vascular remodelling during antiangiogenic tumor therapy using DCE-MRI and vessel size imaging

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Introduction:

Purpose of our study was to assess vascular remodelling in tumors during antiangiogenic therapy with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in combination with vessel size imaging and to evaluate the vessel size index (VSI) as a novel biomarker of therapy response. Thus, nude mice bearing squamous cell carcinoma xenografts were treated with an antiangiogenic therapy and investigated by DCE-MRI and vessel size imaging over time.

Methods:

In total 12 nude mice bearing subcutaneous squamous cell carcinoma xenografts (A431) were investigated with DCE-MRI and vessel size imaging before and after 4 days of treatment. Six animals received antiangiogenic treatment with a selective multitargeted receptor tyrosine kinase inhibitor SU11248 (Sutent® (Sunitinib), Pfizer Inc., NY, USA: 60 mg/kg body weight) for 4 days. To exclude interactions between the different contrast agents DCE-MRI was done at the first day while vessel size imaging was performed at the second day. All MRI experiments were performed on a clinical 1.5 T whole body MR system (Siemens Symphony, Erlangen, Germany) using a custom-made small animal solenoid Tx/Rx radiofrequency coil.

Animal and tumor morphology was assessed using a T1w spin echo sequence and a T2w turbo spin echo sequence. DCE-MRI was performed using a T1w saturation recovery turboFLASH sequence (TR=13ms, TE=5.3ms, TI=300ms, α=12°, averages 4, FOV: 60x22.5mm², voxel size: 0.5x0.5x2mm³). The contrast agent Gadomer (Schering, Berlin; 0.05mmol/kg diluted in 0.9% NaCl to a total volume of 100 µl) was injected via the tail vein. Post-processing was done based on an open two compartment model [1] using the software package DynaLab (Mevis, Bremen, Germany), calculating the parameters Amplitude and k<sub>e</sub>. VSI was calculated by the method published by Troprès et al. [2] using a self implemented VSI Taskcard using RadBuilder. Therefore, T2w images (SE, TR=6000ms, TE=100ms, averages 1, FOV: 60x50.4mm², voxel size: 0.5x0.5x1.5mm³) and a T2* quantification (TR=380ms, TE=4.76-47.6ms (10 inphase echoes), Flip 45°, averages 4, FOV: 60x22.5mm², voxel size: 0.5x0.5x2mm³) was performed before and 3 min after contrast agent administration (Very Small Superparamagnetic Iron Oxide Nanoparticles, VSOP, 200µmol Fe/kg, Ferropharm, Teltow). Large liquid tumor areas, which could not be identified by manual segmentation, were excluded from analysis of DCE-MRI and vessel size imaging data. The changes of the parameters Amplitude, k<sub>e</sub> and VSI were analyzed over time. Differences in vessel density and mean vessel size between treated and untreated tumors were also measured by immunofluorescence.

Results:

The parameter Amplitude decreased significantly (p < 0.01) over time in treated tumors (0.20 ± 0.09 a.u.) compared to untreated ones (0.02 ± 0.08 a.u.), whereas k<sub>e</sub> showed no significant change (treated: 0.28 ± 0.41 1/min; untreated: -0.05 ± 0.25 1/min) (Fig. 1). Also the change of the VSI was capable to mirror antiangiogenic therapy response showing significantly (p < 0.05) higher values in treated than in untreated tumors (Fig. 2). In detail the change of VSI over time of untreated and treated tumors was 7.6 ± 7.7 µm and -3.9 ± 5.4 µm, respectively (Fig. 3). Histological analysis proved the success of the antiangiogenic therapy indicating lower mean vessel area fractions and higher mean vessel size in treated compared to untreated A431 tumors (Fig. 4).

Discussion:

Histological analysis indicated a decrease of CD31 positive area fractions under treatment compared to the control group and thus a decrease in vessel density. Since it was shown previously in a comparative study between contrast-enhanced ultrasound and DCE-MRI that Amplitude highly correlates with the maximum accumulation of microbubbles (which remain strictly intravascular) [3], we postulate that the decrease in Amplitude is caused mainly by the reduction of the relative blood volume. The tendency of k<sub>e</sub> to increase is more difficult to explain and might reflect higher perfusion due to vessel normalisation and higher vessel permeability due to the destruction of immature vessels. The increase in VSI under treatment with the multitargeted tyrosine kinase inhibitor can be explained by a combination of vessel regression and vessel maturation. Histological evaluation indicated that vessel regression mainly occurred for small immature vessels, while larger mature vessels persisted, which is in contrast to larger mean vessel diameters. In conclusion we can firmly state that DCE-MRI and vessel size imaging are in excellent agreement with histology and that the VSI might be a promising biomarker to assess early antiangiogenic therapy response.

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References: